REVIEW

Anticoagulation: Where have we come from and where are we going? The evidence for and against novel anticoagulants

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Warfarin, one of the vitamin K antagonists, has been used since 1940, when it was first approved for the treatment of venous thromboembolism. It is currently the most commonly used anticoagulant, although alternative drugs are available, such as aspirin, clopidogrel and dipyridamol, which have been studied in a number of scenarios. The newest agents available to clinicians are the broad group of novel anticoagulants, such as direct thrombin and direct factor Xa inhibitors, including molecules such as dabigatran, rivaroxaban, apixaban and edoxaban.

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History

Warfarin, one of the vitamin K antagonists (VKAs), has been used since 1940, when it was first approved for the treatment of venous thromboembolism (VTE).[1] The first novel anticoagulant (NOAC) and direct thrombin inhibitor (DTI), lepirudin, originates from 1998, when its intravenous form was approved for the use of clinically relevant heparin-induced thrombocytopenia (HIT).[2] Ximelgatran, the first oral DTI, had a similar clinical efficacy to warfarin, but was withdrawn from the market in 2006 owing to an increased risk of liver toxicity.[3,4] Dabigatran came to the fore in 2009 after the publication of the RE-LY trial in the *New England Journal of Medicine*.[5] This landmark study compared two different doses of dabigatran, 110 mg and 150 mg given twice daily, versus warfarin, in patients with non-valvular atrial fibrillation (NVAF). In summary, this non-inferiority trial showed that dabigatran administered at 150 mg twice daily was associated with lower rates of stroke and systemic embolisation. However, similar rates of major haemorrhage were observed. The RE-LY trial was followed in 2011 by the ROCKET-AF trial, validating the use of rivaroxaban versus warfarin in NVAF. This large randomised controlled trial of more than 14 000 patients confirmed the non-inferiority of rivaroxaban versus warfarin in preventing stroke or systemic embolisation. While there were similar side-effect profiles in each group, the rivaroxaban group appeared to have less intracranial and fatal bleeding. Similar results were shown with apixaban in the ARISTOTLE trial in 2011.[6]

Mechanism of action

Thrombin is central to the clotting cascade and converts fibrinogen to fibrin, thereby creating the framework for clot formation. Thrombin has a number of positive feedback loops that enhance its effect by increasing the effects of factors V, VIII and XI, and also has a procoagulant effect on platelets.[7,8] Furthermore, its procoagulant effects activate factor XIII, which enhances the formation of bonds between fibrin, thereby aiding clot stabilisation. The advantage of DTIs over the indirect thrombin inhibitors such as the heparins is that they are not dependent on antithrombin III. As such, the DTIs can inhibit both free and bound thrombin.[9]

Rivaroxaban, apixaban and edoxaban are very specific antagonists of activated factor Xa, which directly converts prothrombin to thrombin, thus leading to clot formation. Thrombin, in turn, goes on to activate the platelets necessary for the development of a mature clot. Because of the amplifying nature of the clotting cascade, a single molecule of factor Xa is able to generate more than 1 000 molecules of thrombin. Moreover, factor Xa bound to prothrombinase is 300 000 times more active than unbound factor Xa.[10] In summary, activation and binding of factor Xa create a 'clotting explosion', generating massive amounts of thrombin.

Pharmacokinetics

Dabigatran, the prototypical DTI, is a small, highly lipophilic molecule that is rapidly absorbed from the gastrointestinal tract (GIT).[11] Dabigatran undergoes extensive hydrolysis by serum esterases, resulting in only 7% bioavailability.[12] Dabigatran is predominantly metabolised by the kidneys, with 80% being renally excreted as an unchanged molecule.[12] The mean half-life of dabigatran is 8 hours after a single dose and up to 14 hours with multiple twice-daily dosing.[13] As dabigatran is renally eliminated, the half-life increases

dramatically to >24 hours once the creatinine clearance decreases to <30 ml/min.[14]

Factor Xa inhibitors are small molecules that are rapidly absorbed, have good bioavailability after absorption and are highly protein bound, making elimination by dialysis difficult. The factor Xa inhibitors are slightly different from the DTIs in that they are predominantly metabolised in the liver, with 50 - 73% of the dose of the former being excreted via the liver.[15]

An often overlooked pharmacokinetic property of dabigatran and the other factor Xa inhibitors is the effect of an efflux pump on the luminal aspect of the gastrointestinal mucosa. This efflux permeability glycoprotein transporter pump (P-gp) exports dabigatran back into the lumen of the GIT.[13] It would therefore make sense that P-gp inhibitors such as amiodarone, verapamil and quinidine increase the serum concentrations of dabigatran. Conversely, rifampicin, an enzyme-inducer, lowers plasma concentrations by up to 66%.[16]

Monitoring

Warfarin has a narrow therapeutic window with a wide variability in anticoagulant effect, the latter being highly inter- and intrapatient variable.[17] Despite appropriate monitoring, 30 - 50% of international normalised ratios (INRs) remain outside the therapeutic window.[18] One of the main benefits of the pharmacokinetic profile of dabigatran is its predictable renal excretion, with low inter- and intra-individual variability.[11] Clinically, this characteristic allows renal-based dosing without routine monitoring, which is a significant advantage over the VKAs. Dabigatran affects the prothrombin time (PT) and INR, but this is not predictable. While it also affects the activated partial thromboplastin time (aPTT), the concentration-response curve flattens out at higher concentrations and therefore becomes less reliable.[19]

Similar pharmacokinetic and monitoring profiles have been found with the other NOACs) such as rivaroxaban and apixaban.[20] While factor Xa inhibitors do affect the PT, this is unpredictable and unreliable as a quantitative marker of the degree of anticoagulation.

Reversal

Currently, there are no specific reversal agents for dabigatran or the factor Xa inhibitors. As mentioned above, even multidose dabigatran has a relatively short half-life. The most prudent course of action in reversing the effects of the DTIs is to stop administering the agent. The DTIs, including dabigatran, have relatively low protein binding properties; hence a significant amount may be removed during a short session of dialysis.[11] Considering the mechanism of action of the DTIs, it would be appropriate to administer recombinant activated factor VII or prothrombin concentrates. However, these interventions are very expensive and not readily available.

Reversal of VKAs for urgent or invasive surgical procedures is always difficult. Guidelines recommend discontinuing VKAs and starting low molecular weight heparin (LMWH),[11] the latter being discontinued periprocedurally. This results in an approximately 2-week window period during which the patient has variable interruptions in systemic anticoagulation. Interesting results were obtained in the RE-LY trial, analysing a subgroup of patients on dabigatran or warfarin who required an invasive procedure. Patients receiving warfarin were off systemic anticoagulation for a mean of 114 hours. There was no difference in the rates of periprocedural bleeding.[21] In patients requiring emergency surgery, there was a trend to more favourable outcomes in those receiving dabigatran.[21] The results of a randomised controlled trial (BRUISE-CONTROL) of bridging therapy with warfarin versus continuous anticoagulation should provide more direction in the area.[11]

Indications and evidence

Atrial fibrillation

Atrial fibrillation (AF) is the commonest arrhythmia, with an overall prevalence of 5.5%, increasing up to almost 18% in patients >85 years of age.[22] AF is a well-known risk factor for stroke and increases stroke risk approximately 5-fold.[23] More than 20% of strokes are attributable to AF. The 30-day mortality risk is as high as 28% if the condition is left untreated.[24] VKAs have been the standard of care to reduce future risk of stroke. Warfarin decreased the risk of cerebrovascular accidents (CVAs) by 67% and 37% compared with placebo and antiplatelet therapy, respectively.[25] A recent meta-analysis of 50 000 patients requiring anticoagulation for AF provided good evidence for the use of NOACs, with an overall reduction of 11% in mortality and cardiovascular system (CVS)-specific mortality. The number needed to treat (NNT) to prevent one death overall and one cardiovascular death was 244 and 500, respectively.[25] Large trials such as the RE-LY (dabigatran), ROCKET-AF (rivaroxaban) and ARISTOTLE (apixaban) provide the data supporting the use of NOACs in secondary stroke prevention in NVAF. These trials excluded patients with prosthetic valves, mitral stenosis and decompensated heart failure who may have needed valve replacement. The data from these landmark trials cannot therefore be applied to these clinical scenarios. The most recent trial (ENGAGE TIMI-AF 48 trial), studying one of the NOACs (edoxaban), showed non-inferiority of high- and low-dose edoxaban compared with warfarin, but less bleeding and fewer safety end-points in the investigational product groups.[26]

Currently, there are no 'head-to-head' trials comparing dabigatran, rivaroxaban, apixaban and edoxaban. A recent meta-analysis suggests that NOACs are not more effective than warfarin in the secondary prevention of strokes in cases of NVAF. Importantly though, there seems to be a lower risk of intracranial bleeding. In one specific meta-analysis, there did not appear to be a difference in mortality rates.[27] Conflicting data exist and other meta-analyses advocate the use of NOACs, stating that they are more efficacious than warfarin for the prevention of

stroke and systemic embolisation, with a decreased risk of intracranial haemorrhage. There is clearly a knowledge gap that requires a large, comparative, randomised controlled trial to answer these questions. There are no data to support the use of NOACs in patients with a prior history of intracranial, intraocular, spinal, retroperitoneal and intra-articular bleeding, as such patients were excluded.[5,6,28]

Many of the large trials, such as RE-LY and ROCKET-AF, excluded major strokes as well as early strokes in their enrolment of subjects for these novel agents. There seems to be limited literature supporting the early use of these agents in preventing recurrent CVAs or transient ischaemic attacks (TIAs) in patients with AF. A small study reviewed 41 patients who were started on NOACs at a median of 2 days and showed no increase in the incidence of intracranial haemorrhage. However, further data are needed.

In patients who are not candidates for warfarin for stroke prevention in the setting of NVAF, aspirin is often used as an alternative. The AVERROES trial reviewed the use of apixaban versus aspirin in this specific group of patients. The study was discontinued early as there was a clear benefit in favour of apixaban, with similar rates of major bleeding episodes for the two drugs.[29]

There is much debate about whether these agents are cost-effective, particularly in resource-constrained environments. These costs may be US$3 000 per annum for NOACs and US$48 per annum for warfarin.[17] Even taking into account the cost of INR testing and provider visits, the NOACs may be prohibitively expensive. The efficacy data are often clouded by the many single-centre small studies that have often reported no overall or cardiovascular mortality benefit for dabigatran.

The risk profile for major bleeding events seemed to be agent specific. Dabigatran and apixaban were associated with reduced rates of major bleeding, while rivaroxaban was not. [25] Recent evidence in the ENGAGE TIMI-AF 48 trial suggests that edoxaban is not inferior to warfarin with regard to stroke prevention and that it is significantly associated with lower rates of bleeding and death from cardiovascular causes.[26]

Venous thromboembolism

Prophylaxis

There is mounting evidence for the use of dabigatran as a DTI to prevent VTE. The RE-MODEL and RE-NOVATE trials showed that once-daily dabigatran was not inferior to enoxaparin.[30,31] There were no significant differences in the rates of bleeding complications in either knee or hip replacement.

The RECORD-4 trial provided evidence for the use of rivaroxaban prophylaxis in the setting of total knee arthroplasty and was found to be superior to twice-daily enoxaparin in VTE prophylaxis following knee arthroplasty.

The ADVANCE study showed that apixaban was non-inferior to twice-daily enoxaparin in thromboprophylaxis for knee and hip arthroplasty.[32] However, apixaban was superior to once-daily enoxaparin for thromboprophylaxis, with no difference in bleeding events with knee and hip arthroplasty.[32,33]

Venous thrombosis is common in medical patients. Untreated, the incidence of venographically detected thrombosis is about 15%. Unfractionated heparin and LMWH have both been validated for thromboprophylaxis in the medical setting.[34,35] They are highly efficacious, safe, and cost-effective.[36] The role of NOACs in chemical thromboprophylaxis has also been studied. The ADOPT trial was a double-blinded, double-dummy trial comparing apixaban with daily enoxaparin. While there were fewer patients who met the criteria for the primary outcome in the apixaban group, this was not statistically significant. Furthermore, by day 30, there was a significant increase in bleeding complications, including both major and clinically significant non-major bleeding.[37] The MAGELLAN study reviewed a similar role for rivaroxaban in chemical thromboprophylaxis and it would appear that the investigational group showed a reduced rate of thrombo-embolic events. However, this group was treated significantly longer than the control arm that received enoxaparin (35 days of rivaroxaban versus 10 days of enoxaparin).[38] These studies may raise more questions than answers.

Management of confirmed VTE

Dabigatran has also been studied in acute VTE. The RECOVER-I and -II trials showed that fixed-dose management of the condition with dabigatran was non-inferior to warfarin and did not require the intensive monitoring necessary with VKAs.[39,40]

In patients diagnosed with symptomatic deep vein thrombosis (DVT) as well as pulmonary thrombo-embolus (PTE), oral rivaroxaban was non-inferior to warfarin, with similar rates of bleeding.[41,42] Similar evidence now exists for the use of fixed-dose apixaban to treat VTE.[43]

Acute coronary syndromes

Major adverse cardiovascular events (MACEs) are common after acute coronary syndromes (ACSs), notwithstanding optimal care.[44] This is possibly due to the high platelet reactivity, despite dual antiplatelet therapy (DAPT), which may persist for weeks to months after the event.[45,46] While warfarin has been studied as an antiplatelet adjunct post-ACS, this drug had an unacceptable bleeding risk even though it lowered the rate of MACEs.[47] It is therefore important to investigate the role of NOACs in DAPT to prevent MACEs post-ACS. A significant amount of data is now available to study the effects of dabigatran, rivaroxaban, apixaban and darexaban. The addition of NOACs in this setting would seem to confer an unacceptably high risk of haemorrhage, with a 2 - 4-fold increase in the risk of bleeding. There appears to be no clinically significant benefit to the addition of NOACs to DAPT. Further investigation is required to clearly delineate the role of NOACs in ACSs and potentially beneficial combinations

of warfarin, clopidogrel, aspirin, NOACs and new generation P2Y12-receptor inhibitors, such as prasugrel and ticagrelor.

Conclusion

While warfarin and other VKAs have been the gold standard of anticoagulation for over half a decade, the evolution of NOACs has been met with much excitement and has stimulated renewed interest and ongoing research. While biologically attractive, the clinical role of these agents raises many questions regarding how best to integrate them into current treatment regimens. NOACs are more convenient, reliable and predictable than the gold standard. Limitations of using these agents include the cost, lack of a reversal agent and lack of reliable monitoring. With the evidence at hand and considering the cost implications of these drugs, the use of NOACs in a resource-constrained environment seems limited. Should the utility of convenience outweigh the real risks and cost implications of NOACs? The evidence seems to speak for itself.

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